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Supporting Information

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Responsive Cyclohexane-based Low Molecular Weight Hydrogelators with Modular Architecture

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Experimental section

Materials

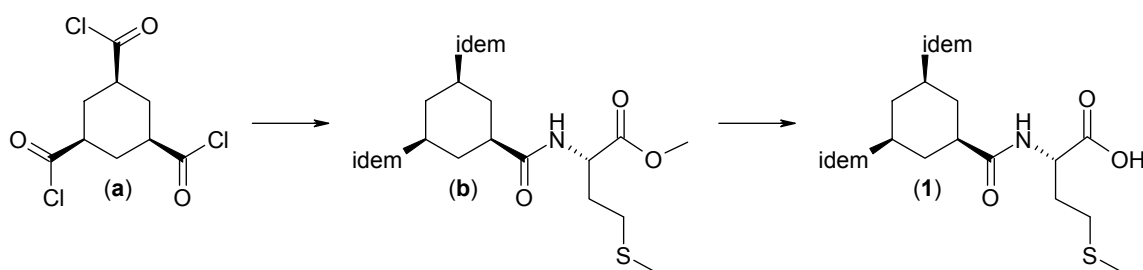
All chemicals were purchased from Aldrich or Fluka and used without further purification. Doubly distilled, deoxygenated water was used for all gelation tests.

Characterization

NMR experiments were performed using a Varian Gemini NMR spectrometer operating at 200 MHz, or a Varian VXR NMR spectrometer operating at 300 MHz. All spectra were recorded in DMSO-d₆ unless stated otherwise. MS-spectra were measured on a JEOL JMS-600H or a Science API 3000 mass spectrometer. Optical rotation measurements were carried out on a Perkin-Elmer 241 Polarimeter, using a Na lamp (589 nm) and DMSO as the solvent. Transmission electron microscopy (TEM) was carried out on a JEOL 1200 EX microscope operating at an accelerating voltage of 80 kV. A lump of a hydrogel was placed on a carbon-coated copper grid (400 mesh) for 1 minute, after which it was removed. The grids were then dried overnight under ambient conditions. No staining or shadowing was applied for the TEM investigation of the hydrogels. All gel-to-sol transition temperatures (T_{gs}) were determined using the “dropping ball” method, which consists in carefully placing a stainless steel ball (65 mg, 2.5 mm in diameter) on top of a gel that had been prepared 16 hours earlier in 2 mL glass vials and subsequently placing these vials in a heating block where the gels can be monitored by means of a CCD camera. The temperature of the heating block is increased by 5 °C per hour and the T_{gs} is defined as the temperature at which the steel ball reaches the bottom of the vial. pH values (pH_{gs}) were

determined by dissolving a weighed amount of the gelator in either an acidic or basic water (HCl or NaOH). Subsequently, small volumes of a slightly basic or acidic solution, respectively, were added until the onset of gelation could be observed (either a thickening of the solution or the appearance of small “gel flakes”), upon which the pH of the solution was measured. The total volume of the gelator solution was then used to calculate the exact gelator concentration. The pH measurements were carried out with a WTW inoLab pH Level 1 meter equipped with a Hamilton minitrode that was calibrated before use.

Synthesis

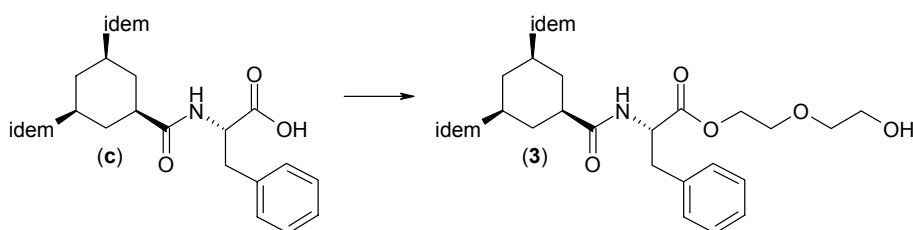


CHex(Met-OMe)₃ (b): To a cooled (0 °C) solution of L-methionine methyl ester hydrochloride (3.22 g, 16.1 mmol) in dry CH₂Cl₂ (200 mL) was added Et₃N (4.5 mL, 32.8 mmol), after which cis,cis-1,3,5-cyclohexanetricarbonyl trichloride (**a**) (1.43 g ; 5.2 mmol) in dry CH₂Cl₂ (15 mL) was added dropwise. After stirring overnight at room temperature a precipitate had formed, which was filtered off and triturated in ethanol and dried to give pure **b**. Yield: 87% (2.96 g; 4.5 mmol). ¹H NMR: δ = 1.45 (t, 1H), 1.76 (d, 1H), 1.91 (m, 2H), 2.03 (s, 3H), 2.30 (t, 1H), 3.62 (s, 3H), 4.37 (q, 1H), 8.21 (d, 1H). ¹³C NMR: δ 13.54, 28.53, 29.36, 30.15, 41.28, 49.70, 50.89, 171.40, 173.48. EI-MS for C₂₇H₄₅N₃O₉S₃ calcd. 651.23; found 651 [M⁺].

CHex(Met-OH)₃ (1): To a cooled (0 °C) suspension of **b** (1.50 g; 2.3 mmol) in MeOH (30 mL), was added aqueous NaOH (15 ml; 2 M). The mixture was slowly brought back to room temperature and stirred for 20 hours. Subsequently, the solution was diluted with water (50 ml) and 2 M HCl was added until the pH was below 3. A precipitate formed that was filtered off, rinsed and dried in the vacuum oven to give pure **1**. Yield: 91% (1.27 g; 2.1 mmol). ¹H NMR: δ = 1.45 (br. q, 1H), 1.71-2.03 (br. m, 4H), 2.03 (s, 3H), 2.30 (br. m, 2H), 3.40 (br. s, OH, 1H), 4.30 (m, 1H), 8.10 (d, 1H). ¹³C

NMR: δ = 13.57, 28.71, 29.57, 30.28, 41.34, 49.66, 172.40, 173.41. Elemental analysis for $C_{24}H_{39}N_3O_9S_3 \cdot 2\frac{1}{2} H_2O$: calcd. C 44.02% H 6.77% N 6.42% O 28.10% S 14.69%; found C 43.89% H 6.88% N 6.26% S 15.15%. EI-MS for $C_{24}H_{39}N_3O_9S_3$ calcd. 609.18; found 610 $[M+H]^+$. $[\alpha]_D^{20}$ = -13.5 (c = 0.99).

CHex(Phe-Gly-OH)₃ (2): Compound **2** was synthesized following the procedure described for compound **1**, using H-Phe-Gly-OMe. Yield (2 steps): 62% (0.34 g, 0.41 mmol). 1H NMR: δ = 1.11 (m, 3H), 1.39 (m, 3H), 2.14 (m, 3H), 2.75 and 3.01 (2 x br. AB, 2 x 3H), 3.79 (br. s, 6H), 4.52 (br. m, 3H), 7.51 (m, 15 H), 8.01 (d, 3H), 8.38 (br. s, 3H). ^{13}C NMR: δ = 29.97, 36.60, 41.10, 52.46, 125.13, 126.88, 128.09, 136.94, 170.06, 170.74, 172.95. EI-MS for $C_{42}H_{48}N_6O_{12}$ calcd. 828.88; found 851.3 $[M+Na]^+$. $[\alpha]_D^{20}$ = -6.8 (c = 1.04).



CHex(Phe-OH)₃ (c): Compound **c** was synthesized following the procedure described for compound **1**, using L-phenylalanine methyl ester hydrochloride. Yield (2 steps): 69% (0.46 g; 0.7 mmol). 1H NMR: δ 1.25 (q, 1H), 1.47 (d, 1H), 2.20 (t, 1H), 2.87 (t, 1H), 3.06 (m, 1H), 4.42 (m, 1H), 7.25 (s, 5H), 8.10 (d, 1H). ^{13}C NMR: δ 30.10, 35.63, 41.16, 52.14, 125.37, 127.09, 128.03, 136.72, 172.16, 173.11. EI-MS for $C_{36}H_{39}N_3O_9$ calcd. 657.27; found 656 $[M-H]^-$.

CHex(Phe-OEtOEtOH)₃ (3): To a suspension of **c** (1.90 g, 2.89 mmol) in diethylene glycol (100 mL) were added a few drops of concentrated HCl. The mixture was stirred at 135 °C for 3 h, after which the now clear solution was added to a water/ice mixture. The gelly precipitate that formed was filtered off and washed with water (3 × 100 mL) and subsequently dissolved in hot MeOH (300 mL). After filtration, the MeOH solution was concentrated and the remaining water was removed by repeated evaporation with toluene (3 × 100 mL). Drying of the remaining white solid *in vacuo* gave pure **5c**. Yield: 75% (2.01 g, 2.18 mmol). 1H NMR: δ = 1.23 (m, 3H), 1.50 (m, 3H), 2.17 (m, 3H),

2.96 (m, 6H), 3.40 (m, 24H: coincides with water peak), 4.11 (br. s, 6H), 4.41 (q, 3H), 4.56 (m, 3H), 7.20 (m, 15H), 8.20 (d, 3H). ^{13}C NMR: δ = 29.93, 35.48, 40.99, 52.26, 59.11, 62.82, 67.00, 71.24, 125.44, 127.12, 127.98, 136.20, 170.63, 173.23. Elemental analysis for $\text{C}_{48}\text{H}_{63}\text{N}_3\text{O}_{15} \cdot 2\text{H}_2\text{O}$: calcd. C 60.18%, H 7.05%, N 4.39%, O 28.39%; found C 60.52%, H 7.09%, N 4.33%. EI-MS for $\text{C}_{48}\text{H}_{63}\text{N}_3\text{O}_{15}$ calcd. 921.43; found 944.5 $[\text{M}+\text{Na}]^+$. $[\alpha]_{\text{D}}^{20} = -8.4$ ($c = 1.03$).

CHex(Phe-NHEtOEtOH)₃ (4): To a cooled (0 °C) solution of H-Phe-NHEtOEtOH \cdot xTFA (3.00 g) and Et_3N (2.10 g; 20.8 mmol = excess) in dry CH_2Cl_2 (100 mL) was added, *cis,cis*-1,3,5-cyclohexanetricarbonyl trichloride (0.40 g; 1.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture. The solution was slowly brought back to room temperature and left to stir overnight. After evaporation of the solvent, the resultant crude was stirred in EtOH, after which the remaining solid was filtered off and dried in a vacuum oven. Recrystallization from water, followed by drying in a vacuum oven gave pure **3d**. Yield: 57% (0.78 g; 0.85 mmol). ^1H NMR: δ = 1.13 (br. q, 3H), 1.39 (br. d, 3H), 2.17 (br. t, 3H), 2.74 (t, 3H), 2.92 (d, 3H), 3.21 (m, 6H), 3.40 (m, 12H), 3.49 (m, 6H), 4.46 (m, 3H), 4.59 (t, 3H), 7.21 (br. m, 15H), 7.98 (d, 3H), 8.05 (m, 1H). ^{13}C NMR: δ = 30.07, 41.02, 52.52, 59.14, 67.84, 71.11, 125.14, 126.88, 128.12, 136.83, 170.32, 172.92, 213.09. Elemental analysis for $\text{C}_{48}\text{H}_{66}\text{N}_6\text{O}_{12} \cdot \text{H}_2\text{O}$: calcd. C 61.52% H 7.31% N 8.97% O 22.20%; found C 61.57% H 7.40% N 8.94%. EI-MS for $\text{C}_{48}\text{H}_{66}\text{N}_6\text{O}_{12}$ calcd. 918.47; found 919.6 $[\text{M}+\text{H}]^+$. $[\alpha]_{\text{D}}^{20} = 2.3$ ($c = 1.09$).

CHex(Met-His-OMe)₃ (5): Compound **5** was synthesized following the procedure described for compound **b**, using H-Met-His-OMe \cdot xTFA (2.76 g). After the reaction a precipitate had formed that was filtered off, washed with CH_2Cl_2 and dried *in vacuo* to give pure **5**. Yield: 53%. ^1H NMR: δ = 1.39 (br. m, 3H), 1.88 (br. m, 9H), 1.99 (s, 9H), 2.36 (br. m, 12H), 2.87 (br. m, 6H), 3.55 (br. m, 6H), 4.35 (br. m, 3H), 4.43 (br. m, 3H), 6.79 (s, 3H), 7.52 (s, 3H), 8.02 (br. m, 3H), 8.32 (br. m, 3H). ^{13}C NMR: δ = 12.55, 27.50, 28.41, 30.64, 37.17, 37.59, 38.01, 38.43, 38.84, 39.26, 39.69, 41.26, 50.30, 50.76, 51.35, 115.24, 132.13, 133.86, 170.37, 170.65, 173.39. Elemental analysis calcd. for $\text{C}_{45}\text{H}_{66}\text{N}_{12}\text{O}_{12}\text{S}_3 \cdot 2\frac{1}{2} \text{H}_2\text{O}$ C 48.77%, H 6.46%, N 15.17%, S 8.68%; found C 48.83%, H 6.57%, N

14.36%, S 8.78%. Mass calcd. for $C_{45}H_{66}N_{12}O_{12}S_3$: 1063.28 found 1063.6 [M]. $[\alpha]_D^{20} = -2.7$ ($c = 1.05$).

CHex(Met-Histamine)₃ (6): A mixture of **1** (1.0 g; 1.64 mmol), carbodiimidazole (0.82g; 5.1 mmol) and Et₃N (0.82 ml; 5.9 mmol) in DMSO (50 mL) was stirred at room temperature for 1 hour. A solution of histamine dihydrochloride (0.94 g; 5.1 mmol) in DMSO (20 mL) was added dropwise and the mixture was stirred overnight. Subsequently H₂O (200 mL) was added and the precipitate that formed was collected by filtration and dried *in vacuo* to give pure **6**. Yield: 45% (0.66 g, 0.74 mmol). ¹H NMR: δ = 1.43 (br. m, 1H), 1.77 (br. m, 3H), 2.02 (br. m, 3H), 2.38 (br. m, 2H), 2.65 (br. m, 2H), 3.29 (br. m, 2H), 4.28 (br. m, 1H), 6.87 (m, 1H), 7.73 (m, 1H), 8.02 (br. m, 2H). ¹³C NMR: δ = 13.58, 25.36, 28.62, 30.74, 41.28, 50.68, 115.52, 132.93, 133.47, 170.08, 173.37. EI-MS for $C_{39}H_{60}N_{12}O_6S_3$ calcd. 889.17 found 889.4 [M⁺]. $[\alpha]_D^{20} = -0.3$ ($c = 1.07$).

CHex(Gly-OH)₃ (7): Compound **7** was synthesized following the procedure described for compound **1**, using H-Gly-OMe. The hydrolysis of the Me-ester, however, was carried out as follows: CHexGlyOMe (0.40 g; 0.9 mmol) was added to MeOH (10 mL). The mixture was cooled and NaOH (5 ml; 2 M) was added, after which the mixture was slowly brought back to room temperature and stirred for 20 hours. The solution was diluted with water (50 ml) and Dowex (H⁺ form) was added until the pH was below 3. The suspension was filtered and the solvent was evaporated *in vacuo*. The resultant solid was dried in the vacuum oven to give pure **7**. Yield (2 steps): 54% (0.28 g; 0.7 mmol). ¹H NMR: δ 1.37 (q, 1H), 1.76 (d, 1H), 2.31 (t, 1H), 3.39 (br, OH, 1H), 3.73 (d, 2H), 8.15 (t, 1H). ¹³C NMR: δ 30.54, 41.26, 170.33, 173.51. Elemental analysis for $C_{15}H_{21}N_3O_9 \cdot 1\frac{2}{3} H_2O$: calcd. C 43.17% H 5.88% N 10.07% O 40.89%; found C 43.03% H 5.67% N 9.70%. EI-MS for $C_{15}H_{21}N_3O_9$ calcd. 387.13; found 386 [M-H]⁻.

CHex(Ser-OH)₃ (8): Compound **8** was synthesized following the procedure described for compound **7**, using H-Ser-OMe. Yield (2 steps): 58% (0.28 g; 0.6 mmol). ¹H NMR: δ 1.42 (d, 1H), 1.80 (d, 1H), 2.38 (t, 1H), 3.44 (br, OH, 1H), 3.67 (m, 2H), 4.28 (d, 1H), 7.93 (d, 1H). ¹³C NMR: δ

30.42, 41.15, 53.50, 60.34, 171.05, 173.37. Elemental analysis for $C_{18}H_{27}N_3O_{12} \cdot 0.5(MeOH + H_2O)$: calcd. C 44.22% H 6.02% N 8.36% O 41.40%; found C 44.29% H 5.77% N 8.21%. EI-MS for $C_{18}H_{27}N_3O_{12}$ calcd. 477.16; found 478 $[M+H]^+$.

Table 1. FT-IR absorptions of NH and CO moieties in gelators **1-6**.

	NH ^a	CO (acid or ester)	CO (amide ^b)	CONH ^c
	solid / xerogel	solid / xerogel	solid / xerogel	solid / xerogel
1	3302, 3301	1711, 1710	1648, 1639	1543, 1459
2	3282, 3287	1727, 1730 ^d	1643, 1631	1542, 1447
3	3293, 3326	1739, 1735	1648, 1639	1539, 1454
4	3284, 3296	---	1642, 1632	1541, 1437
5	3273, 3293	1743, 1742	1638, 1630	1543, 1439
6	3274, 3311	---	1636, 1627	1541, 1439

All absorptions are in cm^{-1} .

^a stretching, secondary amide (trans), hydrogen bonded.

^b stretching, secondary amide, amide I band

^c secondary amide, amide II band

^d very weak absorption

X-ray diffraction: Crystal and Molecular Structure.¹

Abstract: "IUPAC-name", $2(C_{36}H_{39}N_3O_{12}) \cdot 3(H_2O) \cdot 2(HCl)$, $M_r = 1538.40$, triclinic, $P1$, $a = 9.8569(6)$, $b = 14.7887(9)$, $c = 14.8787(9)$ Å, $\alpha = 113.675(1)^\circ$, $\beta = 104.719(1)^\circ$, $\gamma = 101.265(1)^\circ$, $V =$

¹ Supplementary crystallographic data for this paper are available from the IUCr electronic archives (Reference: CCDC 214940). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

1809.66(19) Å³, $Z = 1$, $D_x = 1.412 \text{ g cm}^{-3}$, $F(000) = 810$, $\mu = 1.79 \text{ cm}^{-1}$, $\lambda(\text{MoK}\alpha^-) = 0.71073 \text{ Å}$, $T = 100(1) \text{ K}$, 12183 reflections measured, $\text{Goof} = 1.038$, $wR(F^2) = 0.1257$ for 9630 unique reflections and 1011 parameters, 12 restraints and $R(F) = 0.0509$ for 8089 reflections obeying $F_o \geq 4.0 \sigma(F_o)$ criterion of observability.

The asymmetric unit consists of seven moieties: two molecules of the title compound, two of HCl and three H₂O solvent molecules.

Small needle-shaped (bunches of needles) crystals were obtained by recrystallisation from dilute HCl. Although an X-ray structure determination was thwarted by persistent weak scattering power of the crystals, ultimately there was found a crystal fit to the X-ray experiment.

A colorless colored block-shaped crystal with the dimensions of 0.12 x 0.09 x 0.09 mm was mounted on top of a glass fiber and aligned on a *Bruker*¹ *SMART APEX CCD* diffractometer (Platform with full three-circle goniometer). The diffractometer was equipped with a 4K *CCD* detector set 60.0 mm from the crystal. The crystal was cooled to 100(1) K using the *Bruker KRYOFLEX* low-temperature device. Intensity measurements were performed using graphite monochromated Mo-K α^- radiation from a sealed ceramic diffraction tube (*SIEMENS*). Generator settings were 50 KV/ 40 mA. *SMART* was used for preliminary determination of the unit cell constants and data collection control. The intensities of reflections of a hemisphere were collected by a combination of 3 sets of exposures (frames). Each set had a different ϕ angle for the crystal and each exposure covered a range of 0.3° in ω . A total of 1800 frames were collected with an exposure time of 30.0 seconds per frame. The overall data collection time was 17.9 h. Data integration and global cell refinement was performed with the program *SAINT*. The final unit cell was obtained from the xyz centroids of 3060 reflections after integration. Intensity data were corrected for Lorentz and polarization effects, scale variation, for decay and absorption: a multi-scan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (*SADABS*)², and reduced to F_o ². The program suite *SHELXTL* was used for space group determination (*XPREP*).¹

The unit cell³ was identified as triclinic; space group *P*1. The $|E|$ distribution statistics were indicative of a non-centrosymmetric space group.⁴ Reduced cell calculations did not indicate any higher metric lattice symmetry⁵ and examination of the final atomic coordinates of the structure did not yield extra crystallographic or metric symmetry elements.^{6,7}

The structure was solved by direct methods with *SIR-97*.⁸ The positional and anisotropic displacement parameters for the non-hydrogen atoms were refined. Some atoms showed unrealistic displacement parameters when allowed to vary anisotropically, suggesting dynamic disorder (dynamic means that the smeared electron density is due to fluctuations of the atomic positions within each unit cell) as a consequence of the configurational- and rotational- disorder. This is in line with the weak scattering power of the crystals investigated.

The smeared electron density for O111 has been described by two site occupancy factors with separately refined displacement parameters. The s.o.f. of the major fraction of the component of the disorder model refined to a value of 0.663(11).

Most of the hydrogen atom positions were generated (!) by geometrical considerations, except for the Cl moieties (probably dissociated; so not included), and included in the final refinement riding on their carrier atoms and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms.

Final refinement on F^2 carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.1257$ for 9630 reflections and $R(F) = 0.0509$ for 8089 reflections with $F_o \geq 4.0 \sigma(F_o)$ and 1011 parameters and 12 restraints. The final difference Fourier map was essentially featureless, except one free peak of 1.06(6) e/Å³ (more than 2.5 Å from closest atom (1.06(6) e/Å³) position), but was neglected/rejected, being an artifact. No other significant peaks (max. = 0.51(6) e/Å³) having chemical meaning above the general background were observed in the final difference Fourier syntheses.

The X-ray data allowed determination of the absolute stereochemistry: the absolute structure actually chosen was determined by Flack's^{9,10,11,12} *x*-refinement (*x* = -0.20(7)). All chiral C centers showed the S-configuration.

The positional and anisotropic displacement parameters for the non-hydrogen atoms and isotropic displacement parameters for hydrogen atoms were refined on F^2 with full-matrix least-squares procedures minimizing the function $Q = \sum_h [w(|(F_o^2) - k(F_c^2)|)^2]$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, $P = [\max(F_o^2, 0) + 2F_c^2] / 3$, F_o and F_c are the observed and calculated structure factor amplitudes, respectively; ultimately the suggested a ($=0.0735$) and b ($= 0.0$) were used in the final refinement. Neutral atom scattering factors and anomalous dispersion corrections were taken from *International Tables for Crystallography*.¹⁵ All refinement calculations and graphics were performed on a Pentium-III / Debian-Linux computer at the University of Groningen with the program packages *SHELXL*¹⁶ (least-square refinements), a locally modified version of the program *PLUTO*¹⁷ (preparation of illustrations) and *PLATON*¹⁴ package (checking the final results for missed symmetry with the *MISSYM* option, solvent accessible voids with the *SOLV* option, calculation of geometric data and the *ORTEP*¹⁴ illustrations).

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